A DOUBLE-BLIND, ASCENDING SINGLE AND MULTIPLE DOSE, SAFETY, TOLERABILITY, PHARMACOKINETIC, PHARMACODYNAMIC AND FOOD EFFECT STUDY OF EVP 6308 IN HEALTHY VOLUNTEERS.

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Primary:to evaluate the safety and tolerability of EVP-6308 after single and multiple ascending dose administration in healthy subjects.Secondary:to determine the pharmacokinetics of EVP-6308 and select metabolites following single and multiple oral...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Schizophrenia and other psychotic disorders
Study type	Interventional

Summary

ID

NL-OMON37679

Source
ToetsingOnline

Brief title
EVP-6308 single and multiple ascending dose study.

Condition

- Schizophrenia and other psychotic disorders

Synonym
delusions, schizophrenia

Research involving

Human

Sponsors and support

Primary sponsor: EnVivo Pharmaceuticals, Inc.
Source(s) of monetary or material Support: Pharmaceutische industrie.

Intervention

Keyword: EVP-6308, Food Effect, Multiple Ascending Dose, Single Ascending Dose

Outcome measures

Primary outcome

Safety: AEs, vital signs, 12-lead ECG, clinical laboratory, prolactin, inhibin

B and physical examination

Secondary outcome

PK : plasma concentrations of EVP 6308 and select metabolites, plasma and urine

PK parameters; metabolite profiling of plasma if conducted, will be reported

separately.

PD : qEEG, Bond and Lader VAS and DSST

Study description

Background summary

EVP-6308 is a new investigational compound that may eventually be used for the treatment of schizophrenia. This is the first time that this compound is being given to humans.

EVP 6308 is a selective phosphodiesterase (PDE) 10A inhibitor being developed to treat the positive (such as hallucinations and delusions), negative (such as flattened affect, sexual dysfunction and social withdrawal), and cognitive symptoms of schizophrenia.

As described in depth in the EVP 6308 Investigator*s Brochure2, there are several lines of evidence, both neurochemical and behavioral, which suggest

that PDE-10A inhibition may decrease both positive and negative symptoms of schizophrenia as well as improve cognitive performance. Therefore, PDE10A inhibitors are potentially a broad spectrum therapy to treat all symptom domains (positive, negative and cognitive) of schizophrenia.

Study objective

Primary:
to evaluate the safety and tolerability of EVP-6308 after single and multiple ascending dose administration in healthy subjects.

Secondary:
to determine the pharmacokinetics of EVP-6308 and select metabolites following single and multiple oral dose administration of EVP-6308;

to assess the pharmacodynamic effects of EVP-6308 on the central nervous system using quantitative electroencephalogram analysis, a Digit Symbol Substitution Test and a subjective mood measurement;

to assess whether the pharmacokinetics of EVP-6308 is affected by food.

Study design

A double-blind, randomized, placebo-controlled study, consisting of a single ascending dose (SAD) with integrated food
effect part, and a multiple ascending dose (MAD) part. In the SAD part,

Cohorts 1 and 2 with 8 subjects (6 subjects on active and 2 on placebo) will be treated with escalating doses in an alternating panel design with a washout of at least 14 days between dose administrations. In the first dose cohort, for risk mitigating purposes, initially 2 subjects (one active, one placebo) will be dosed and after a 24-hour safety monitoring window, the remainder of the first cohort will be dosed.
Cohort 3 with 6 subjects (6 subjects on active) will be treated with one dose level; In the MAD part, 4 groups of 12 subjects (9 subjects on active and 3 on placebo) will be treated with escalating sequential doses.

Procedures and assessments SAD part:
Screening :
demographics, medical history, clinical laboratory (including clinical chemistry, hematology and urinalysis), pregancy test
(females), fecal occult blood test, physical examination (including height and body weight), vital signs (including supine
systolic and diastolic blood pressure, pulse rate, oral body temperature and respiration rate), 12-lead electrocardiogram
(ECG), screening electroencephalogram (EEG), drug and alcohol screen, HBsAg,

anti HCV, anti-HIV 1/2, adverse events
(AEs), previous and concomitant medication

Observation period:
Groups 1 and 2: three periods in the clinic, each being from Day -1 until 48 h (Day 3) after drug administration;
Group 3: one period in the clinic from Day -1 until 48 h (Day 3) after drug administration,
Group 4 - 7: one period in the clinic from Day -1 until 48 h after the last drug administration on Day 14.

Blood sampling:
During this study less then 450 ml of blood will be drawn. It is anticipated for Part 1 and 2 that in every period an indwelling canula will be inserted for most of the blood sampling Day -1 and Day 1, on the other Days blood will be drawn by direct puncture of the vein. It is anticipated for Part 3 that an indwelling canula will be used on Days -1 and Day(s) 1, 7, 14. On the other days blood will be drawn by direct puncture of the vein.

Collection of urine:
Urine will be collected in each Period at pre-dose and in intervals until 24-48 hrs hours after administration of EVP-6308 (thus until Day 3).

Pharmacodynamic tests:
Bond and Lader Visual Analog Scale (VAS): Only in SAD and MAD. This is a questionnaire where you are asked to rate items related to alertness, calmness and contentment .SAD: in each Period at set intervals and in MAD: on Days 1 and 14 at set intervals.

Digit Symbol Substitution Test (DSST test): Only in SAD and MAD. The DSST is a test in which you will asked to substitute figures
by symbols. SAD: in each Period at set intervals and in MAD: on Days 1 and 14 at set intervals.

Screening EEG and Quantitative (q)EEG: Only in MAD. (EEG) will be recorded at regular intervals using standardized devices on Days 1 and 14.

Safety:
AEs: recorded from the time the Informed Consent Form (ICF) is signed until completion of the follow up visit; clinical
laboratory (including clinical chemistry, hematology and urinalysis): each period at 48 h post-dose; vital signs (including
supine systolic and diastolic blood pressure, pulse rate, oral body temperature and respiration rate): each period at predose
and at 1, 2, 3, 4, 5, 6, 8, 24 and 48 h post-dose; 12-lead ECG: each period at 1, 4, 8, 24, and 48 h post-dose,

physical examination: each period at 48 h post dose.

Intervention

SAD part:
Group 1 Period 1: a single oral dose of 5 mg EVP 6308 (n=6) or matching placebo (n=2) under fasted conditions
Period 2: a single oral dose of 20 mg EVP 6308 (n=6) or matching placebo (n=2) under fasted conditions
Period 3: a single oral dose of 100 mg EVP 6308 (n=6) or matching placebo (n=2) under fasted conditions
Group 2 Period 1: a single oral dose of 10 mg EVP 6308 (n=6) or matching placebo (n=2) under fasted conditions
Period 2: a single oral dose of 50 mg EVP 6308 (n=6) or matching placebo (n=2) under fasted conditions
Period 3: a single oral dose of 200 mg EVP 6308 (n=6) or matching placebo (n=2) under fasted conditions

FE part:
Group 3 Period 1: a single oral dose of X mg EVP 6308 (n=6) under fasted conditions
Period 2: a single oral dose of X mg EVP 6308 (n=6) under fed conditions

MAD part:
Group 4 multiple oral doses of 20 mg EVP 6308 (n=9) or matching placebo (n=3) for 14 days under fasted or fed conditions
Group 5 multiple oral doses of 50 mg EVP 6308 (n=9) or matching placebo (n=3) for 14 days under fasted or fed conditions
Group 6 multiple oral doses of 100 mg EVP 6308 (n=9) or matching placebo (n=3) for 14 days under fasted or fed conditions
Group 7 multiple oral doses of 200 mg EVP 6308 (n=9) or matching placebo (n=3) for 14 days under fasted or fed conditions

Study burden and risks

Procedures : pain, light bleeding, heamatoma, possibly an infection.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Age : SAD part (Groups 1-3) and MAD part (Groups 4-7): 18-65 years, inclusive;
BMI : 18.0 * 28.0 kg/m2, inclusive
Gender : healthy male or female subjects; female subjects must be of non-childbearing potential (either surgically
sterilized or at least 1 year post-menopausal)

Exclusion criteria

Suffering from : hepatitis B. cancer or HIV/AIDS. In case of participation in another drug study within 60 days before the start of the study. In case of donating blood or significant loss of blood within 60 days of the start of drug dosing.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-05-2012
Enrollment:	70
Type:	Actual

Ethics review

Approved WMO Date:	04-05-2012
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-05-2012
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-001319-22-NL
CCMO	NL40413.056.12